REVIEW ARTICLE

New oral anticoagulants: not quite there yet

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KEY WORDS

apixaban, dabigatran, oral anticoagulants, rivaroxaban, vitamin K antagonists (VKA)

ABSTRACT

The results of 3 large randomized trials of activated factor X inhibitors, for the prevention of venous thromboembolism, recently became available. Similar data for orally active thrombin inhibitors is also available from recent trials. In this review, we attempt to provide a balanced perspective on the relative merits and demerits of the new, orally active anticoagulants, and speculate on the future of these agents in clinical practice.

Anticoagulants are pivotal agents in the prevention and treatment of thromboembolic disorders.[1,2] Currently, parenteral agents are used to prevent and treat acute thromboembolic disorders, often in hospital, while oral agents (coumarins) are used for long-term anticoagulation.[2] For over the past 65 years, the vitamin K antagonists (VKA), such as warfarin have been the only oral anticoagulants available. Vitamin K antagonists are effective for the prevention and treatment of venous thromboembolism (VTE), for the prevention of systemic embolism from a cardiac source (e.g. in atrial fibrillation and valvular heart disease) and for the extended treatment of myocardial infarction.[3] These agents, however, have important limitations, including drug and food interactions that lead to a variable anticoagulant response, which in turn leads to the requirement for frequent anticoagulant monitoring.[3] Anticoagulant monitoring is labor intensive and can be stressful for a patient and health care professional. For this reason, there is an important need for a replacement for VKA, which can be administered orally without the need for anticoagulant monitoring. This need has stimulated the development of orally-active, synthetic small molecules that target specific clotting enzymes.

Three obstacles had to be overcome before new oral anticoagulants that do not require coagulation monitoring could be developed. The first was to elucidate the structure of the active site of clotting enzymes and design small molecules to fit into the active site like a key into a lock. The second was to design ways to protect these small molecules from inactivation while they were being absorbed from the gastrointestinal tract. And the third was to ensure that safe and effective levels of the drug could be achieved without routine dose adjustment.

Several small molecular weight oral inhibitors that either target thrombin or factor Xa are in advanced stages of clinical development.[4] These compounds do not appear to be affected by food intake, have a low potential for drug interactions and, because they have a much more predictable dose response than VKAs, they are administered in fixed doses without anticoagulant monitoring. Results of earlier clinical trials with direct parenteral[5] and oral thrombin inhibitors[6] and indirect parenteral factor Xa inhibitors[7] have validated both thrombin and activated factor X as promising targets for new oral anticoagulants. More recently, the results of phase 3 clinical trials with these new oral inhibitors suggest that these oral agents are likely to be safe and effective when used in fixed doses without routine anticoagulant monitoring.[8-10] These recent clinical findings provide hope that more convenient, effective and safe oral anticoagulants will soon be available to replace VKAs.

The greatest need for new oral anticoagulants is for prevention of cardioembolism in patients with atrial fibrillation (AF) or prosthetic heart valves.[3] Since, however, the cost to develop a new anticoagulant is high, clinical drug development often starts with studies in the prevention of venous thrombosis because the required sample size is much smaller and the duration of follow-up is shorter. Such an approach presupposes that

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Received: October 28, 2008.
Accepted: October 30, 2008.
Conflict of interest. Dr Eikelboom has the following disclosures: consulting fees and/or honoraria: Astra Zeneca, Boehringer Ingelheim, Bristol Myer Squibb, Corgenix, Daiichi Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Haemoscope, McNeil, Sanofi Aventis; grants and/or in-kind support: Accumetrics, Aspirin Works, Bayer, Boehringer Ingelheim, Bristol Myer Squibb, Corgenix, Dade Behring, GlaxoSmithKline and Sanofi Aventis.
Pol Arch Med Wewn. 2009; 119 (1-2): 53-59

TABLE 1 Phase III studies comparing dabigatran and enoxaparin in patients undergoing joint replacement surgery

	REMODEL[8]	RENOVATE[9]	REMOBILIZE[10]
Surgery	Knee replacement	Hip replacement	Knee replacement
Dabigatran – dose and timing of administration	220/150 mg/d 1–4 hours after surgery[a]	220/150 mg/d 1–4 hours after surgery[a]	220/150 mg/d 6–12 hours after surgery[a]
Enoxaparin – dose and timing of administration	40 mg once daily, evening before surgery	40 mg once daily, evening before surgery	30 mg twice daily, 12–24 hours after surgery
Duration of study treatment	6–10 days	28–35 days	12–15 days
Primary outcome (%)[b]			
Dabigatran 220 mg	36.4	6.0	31.1
Dabigatran 150 mg	40.5	8.6	33.7
Enoxaparin arm	37.7	6.7	25.3
Major bleeding (%)[c]			
Dabigatran 220 mg	1.5	2.0	0.6
Dabigatran 150 mg	1.5	1.3	0.6
Enoxaparin arm	1.3	1.6	1.4
Trial result (efficacy)	Dabigatran non-inferior to enoxaparin	Dabigatran non-inferior to enoxaparin	Dabigatran inferior to enoxaparin

a Started at half the dose

b Composite of total VTE and all-cause mortality

c The definitions of major bleeding were different in the dabigatran studies and the rivaroxaban studies, contributing to the large differences in bleeding

success in the prevention of VTE predicts success for other indications.

The first orally-active drug to be evaluated clinically was the thrombin inhibitor ximelagatran, which is a pro-drug that after absorption from the small intestine undergoes rapid biotransformation to melagatran, the active agent. Ximelagatran has a plasma half-life of 4 to 5 hours and is administered orally twice daily.[11] Based on its predictable anticoagulant response, ximelagatran was administered in fixed doses without coagulation monitoring and evaluated in large phase 3 trials for thromboprophylaxis in high-risk orthopedic patients, for treatment of VTE and for prevention of cardioembolic events in patients with non-valvular atrial fibrillation.[12] These studies showed that ximelagatran:

1 administered post-operatively is safe and effective for the prevention of venous thrombosis in patients undergoing elective orthopedic surgical procedures

2 is an effective and safe alternative to low molecular-weight heparin (LMWH) followed by warfarin, for acute treatment of VTE

3 is as effective and safe as warfarin for the prevention of stroke in patients with atrial fibrillation.[12]

Unfortunately, because of hepatic toxicity, the clinical development of ximelagatran was discontinued.[13] However, the results of the clinical trials with ximelagatran were ground-breaking because, for the first time they showed that a rapidly acting oral anticoagulant can be used without coagulation monitoring, and that when used in such a manner, it had the potential to replace coumarins, and so greatly improve the convenience of long-term anti-coagulant therapy.

In the remainder of this review we will discuss the current status of the three most advanced new oral anticoagulants, two factor Xa inhibitors and a factor IIa inhibitor, and speculate on their future role in clinical practice.

Current status **Dabigatran etexilate** Dabigatran etexilate is an oral direct thrombin inhibitor, which is converted into its active metabolite, dabigatran, after absorption from the gastrointestinal tract.[14] Bioconversion begins in the gut and is completed in the liver. The drug has low oral bioavailability (about 6%), and relatively high doses need to be given to achieve adequate plasma concentrations. Absorption is dependent upon an acid environment and is reduced by 20–25% if proton pump inhibitors are given concomitantly.[15] Plasma levels of dabigatran peak 2 hours after oral administration and the half-life is 12 to 17 hours in patients with preserved renal function making single daily dosing possible.[4] About 20% of the drug is conjugated and excreted via the biliary system and the remaining 80% is excreted unchanged by the kidneys.[14,15] Dabigatran etexilate is therefore contraindicated in patients with renal insufficiency. The cytochrome P450 system is not involved in the metabolism of dabigatran etexilate. Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein and reduced doses are recommended in patients treated with amiodarone. Quinidine is contraindicated in patients treated with dabigatran etexilate.

An early dose ranging study of dabigatran etexilate in patients undergoing hip replacement surgery found the drug to be effective over a wide spectrum of doses between 12.5 mg to 300 mg per day.[16] A subsequent large phase II study

TABLE 2 Phase III studies comparing rivaroxaban and enoxaparin in patients undergoing joint replacement surgery

	RECORD 1	RECORD 2	RECORD 3	RECORD 4
Surgery	Hip replacement	Hip replacement	Knee replacement	Knee replacement
Rivaroxaban – dose and timing of administration	10 mg once daily 6–8 hours after wound closure	10 mg once daily 6–8 hours after wound closure	10 mg once daily 6–8 hours after wound closure	10 mg once daily 6–8 hours after wound closure
Enoxaparin – dose and timing of administration	40 mg enoxaparin once daily, 12 hours before surgery	40 mg enoxaparin once daily, 12 hours before surgery	40 mg enoxaparin once daily, 12 hours before surgery	30 mg twice daily, 12–24 hours after surgery
Duration of study treatment	31–39 days	Rivaroxaban 31–39 days Enoxaparin 10–14 days	10–14 days	10–14 days
Primary outcome (%)[a]				
Rivaroxaban	1.1	2.0	9.6	6.9
Enoxaparin	3.7	9.3	18.9	10.1
Major bleeding (%)[b]				
Rivaroxaban	0.3	<0.1	0.6	0.7
Enoxaparin	0.1	<0.1	0.5	0.3
Trial result (efficacy)	Rivaroxaban superior	Rivaroxaban superior	Rivaroxaban superior	Rivaroxaban superior

a Composite of total VTE and all-cause mortality

b The definitions of major bleeding were different in the dabigatran studies and the rivaroxaban studies, contributing to the large differences in bleeding

of patients undergoing hip or knee replacement, evaluated doses between 50 and 300 mg and found that there was a significant dose-related decrease in the occurrence of VTE and increase in major bleeding with higher doses. The 150 mg and 225 mg twice daily doses appeared to offer the best efficacy.[6] However, subsequent phase III trials all evaluated both 150 mg and 220 mg of dabigatran etexilate, given once a day.[8-10] In a meta-analysis of the phase II and phase III studies (total of 4 studies and nearly 7000 patients), dabigatran 150 or 220 mg/d was similarly effective to enoxaparin for prevention of venous thromboembolism (risk ratio [RR] 1.06, 95% CI 0.97–1.16, p = 0.22) with no increase in bleeding (unpublished data). The interpretation of these results is complicated by differences in the patient population studied in these trials, the dose and timing of administration of the study drugs, and the duration of study therapy (TABLE 1). The most important difference between the trials pertained to the dose and timing of enoxaparin administration, because of the differing practices in North America and Europe. The one trial that compared dabigatran etexilate with the North American, enoxaparin 30 mg twice daily dosing strategy showed that dabigatran etexilate was inferior to enoxaparin.[10]

Dabigatran etexilate given in a dose of 50 mg, 150 mg or 300 mg twice daily has been compared to warfarin (adjusted to an international normalized ratio [INR] of 2–3) in a dose-finding study of 502 patients with AF.[17] In a second randomization, patients treated with dabigatran were also assigned to receive aspirin 81 mg or 325 mg once daily or placebo in a factorial design. The combination of aspirin and the 300 mg twice daily dose of dabigatran etexilate was associated with increase in major bleeding and was therefore discontinued. Patients were then followed in an open-label fashion for a period of 16 months.[18] The best combination of efficacy and safety was observed with the 150 mg twice daily dose. Based on this experience, the ongoing, pivotal, phase III RELY study has randomized 18,000 patients to either dabigatran etexilate 110 mg or 150 mg, twice daily, or adjusted dose warfarin (INR 2–3). The study is expected to be reported in September 2009. This trial should provide definitive answers regarding the efficacy and safety of dabigatran etexilate in the prevention of thromboembolism in high-risk patients with AF.

Rivaroxaban Rivaroxaban binds selectively to the active site of factor Xa, regardless of whether it is free or bound within the prothrombinase complex. The drug inhibits the enzyme in a competitive and reversible fashion.[19] Bioavailability is more than 80% after an oral dose and is unaffected by food. Peak plasma concentrations are achieved in about 3 hours and half-life in plasma is 9 hours.[15] The half life may be prolonged in the elderly. Two-thirds of the drug is excreted via the kidneys and the remaining in feces. Like dabigatran etexilate, rivaroxaban is contraindicated in patients with renal insufficiency. Gastrointestinal excretion of rivaroxaban is mediated by P-glycoprotein. It is metabolized in the liver, at least partly by cytochrome P450 (CYP) -dependent mechanisms. Therefore, inhibitors of CYP3A4 and P-glycoprotein (e.g. ketoconazole, ritonavir) may cause plasma drug levels to rise.[15]

Two early dose-finding studies evaluated rivaroxaban in patients undergoing hip or knee replacement surgery.[20,21] These studies demonstrated a flat dose response relationship in efficacy for prevention of VTE but a dose-dependent

increase in the risk of bleeding. The optimal dose was considered to be between 5 and 20 mg/d. In another phase II study in patients undergoing hip replacement, similar results were found, thereby leading to evaluation of a dose of 10 mg/d in phase III trials.[22]

To date, 4 phase-III trials of rivaroxaban in VTE prophylaxis have been completed, and all of them have demonstrated superiority of rivaroxaban over enoxaparin in preventing VTE.[23-26] Meta-analysis of the available data (7 studies and over 7000 patients) with rivaroxaban indicates that it is superior to enoxaparin in preventing VTE (RR 0.48, 95% CI 0.41–0.57, p <0.001) but that rivaroxaban increases clinically relevant non-major bleeding (unpublished data). Similar to the trials of dabigatran, the rivaroxaban trials differed substantially in terms of the populations studied, the dose and timing of administration of the study drugs, and the duration of study therapy (TABLE 2). The shorter duration of treatment specified for the enoxaparin arm compared to the rivaroxaban arm in the RECORD 2 study contributed to the large difference in treatment effect in this trial (TABLE 2).[24] The observed benefits of rivaroxaban compared with enoxaparin were less in the RECORD 4 study where the (higher) North American twice-daily dosing regimen for enoxaparin was used. Further, the much lower than usual rates of VTE in control patients undergoing knee replacement in the RECORD 3 and 4 studies,[25,26] suggests that these studies included a lower risk population.

Rivaroxaban has also been evaluated for the treatment of deep venous thrombosis (DVT) in 2 Phase II studies. Both studies tested multiple doses of rivaroxaban against a regimen of short-term enoxaparin followed by oral vitamin K antagonist, given for a period of 3 months. Rivaroxaban reduced thrombus burden as measured by serial ultrasound,[27] and the occurrence of a composite of VTE-related death, DVT or pulmonary embolism.[28] As with the VTE prevention studies there was no dose-response with respect to efficacy. A 20 mg qd dose is being evaluated in the ongoing phase III studies in the treatment of VTE and for prevention of stroke in AF.

Apixaban Apixaban is a small molecule which selectively and reversibly inhibits factor Xa. Like rivaroxaban, it inhibits both free and bound factor Xa. The drug has an oral bioavailability of 50% which is unaffected by food, and a terminal plasma half-life of 9–14 hours after repeated dosing.[29] It is metabolized in the liver by both CYP3A4 and CYP-independent mechanisms. The drug is mainly excreted in the feces, with the renal route accounting for about 25% of elimination.[29] The potential for drug interactions with apixaban is similar to that with rivaroxaban.

A phase II, dose-ranging study compared apixaban with enoxaparin or warfarin in patients undergoing knee replacement surgery.[30] This study included 1238 patients who were randomized in a double-blind manner to 1 of 6 apixaban doses (5, 10 or 20 mg/d administered as a single or a twice-daily divided dose), enoxaparin (30 mg twice daily) or open-label warfarin (titrated to an INR of 1.8–3.0). Apixaban and enoxaparin were initiated 12–24 hours after surgery and warfarin was started on the evening before surgery. Treatment was continued for 10–14 days. Compared to enoxaparin or warfarin, all doses of apixaban reduced the occurrence of the primary endpoint (which was a composite of VTE diagnosed by mandatory venography, and all cause mortality). There was a dose-dependent increase in efficacy, but also a significant dose-related increase in the incidence of total adjudicated bleeding events. Based on the results of this study, a dose of 2.5 mg twice daily or 5 mg once daily has been selected for investigation in phase III trials. Apixaban has also been evaluated in a dose ranging study among patients with symptomatic DVT. In this study apixaban (5 mg bd, 10 mg bd or 20 mg qd) was compared with LMWH followed by oral VKA therapy for a total of 84–91 days.[31] The occurrence of the primary outcome event (a composite of recurrent symptomatic venous thromboembolism and asymptomatic deterioration of bilateral compression ultrasound or perfusion lung scan) was similar in the apixaban and the LMWH/VKA group with no evidence of a dose-response relationship with apixaban. The occurrence of the principal safety outcome (a composite of major and clinically relevant non-major bleeding) was also similar in the two treatment groups.[31]

In the only completed phase III study of apixaban for VTE prevention involving 3195 patients undergoing knee replacement surgery, apixaban 2.5 mg given twice daily compared with enoxaparin 30 mg twice daily did not meet statistical criteria for noninferiority but significantly reduced bleeding. The rates of the composite primary end-point (any VTE or all-cause death) were numerically similar between the two treatments (9.0% vs. 8.9%).[32] Major bleeding was less frequent (0.7% vs. 1.4%, p = 0.053) and clinically relevant bleeding was significantly lower among patients receiving apixaban (2.9% vs. 4.3%, p = 0.034).[32] Further details are expected when the study results will be presented later this year.

The future of oral factor Xa and thrombin inhibitors

The results of phase III trials of dabigatran etexilate, rivaroxaban and apixaban are promising for VTE prevention in patients undergoing orthopedic surgery. Unlike VTE prevention in orthopedic surgery where parenteral agents are likely to retain a major role, orally administered VKAs are the antithrombotics of choice in patients with AF, in those with prosthetic heart valves, and in those requiring continued out-of-hospital treatment for secondary prevention of VTE. Therefore, a clearer picture of the clinical utility of new oral anticoagulants will become apparent only when the results of the large ongoing phase III trials

in patients with AF and in those with established VTE become available. Based on experience with VKAs, it is likely that an oral agent that is effective for any one of these indications has the potential to be effective and safe for the others. Since, however, the optimal dosing regimens for the various anticoagulants are likely to vary from one indication to the next, a potentially valuable drug could be discarded and lost from clinical practice if it is evaluated using a sub-optimal dose. Past experience with parenteral inhibitors indicates that both oral factor Xa and thrombin inhibitors will be effective for most indications. An exception might exist for prosthetic heart valves in which the contact activation pathway is likely to contribute to thrombogenesis. This prediction is based on the failure of fondaparinux (a parenteral factor Xa inhibitor) to prevent catheter-related thrombosis in the acute coronary syndrome trials.[33,34] and its parallel inability to inhibit contact pathway activation of the coagulation cascade.[35] On the other hand, thrombin inhibition (using bivalirudin) does not appear to be associated with catheter-related thrombosis.[36] On the basis of these observations, it is conceivable that factor Xa inhibitors might be less effective than thrombin inhibitors (like dabigatran) in preventing thromboembolic complications in patients with mechanical heart valves.

In addition to the efficacy and safety demonstrated in the VTE prevention trials, the long-term safety and cost will also determine the acceptance and uptake of new oral anticoagulants into clinical practice. Dabigatran etexilate and rivaroxaban have been approved for use in Europe and Canada and are priced similarly to prophylactic doses of LMWH. Additional efficacy data as well as long-term safety data will be obtained from phase III trials in patients with AF and VTE that are either in the later stages of completion or currently ongoing.

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